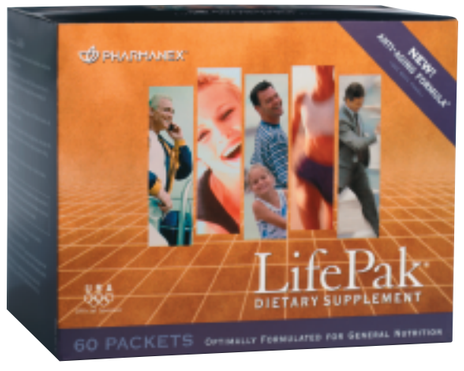
LifePak®

Healthcare Professional Product Guide



This is an educational publication provided to help licensed healthcare professionals understand the science upon which LifePak is based and the nutrient content mechanisms of action in the body. This guide should not be used to sell LifePak and is intended for healthcare professionals only.

The only claims that can be made for LifePak are those that have been approved by the Company.

A Scientific Product Review

High quality comprehensive multi-nutrient supplement

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LifePak®

High quality comprehensive multi-nutrient supplement

Summary

LifePak is a comprehensive multivitamin/mineral/phytonutrient supplement designed to promote general health and well-being.* LifePak addresses all common nutrient deficiencies, provides the key anti-aging nutrients that promote cellular protection and regeneration, and supports cardiovascular health, bone metabolism, insulin and blood glucose metabolism, and normal immune function.* LifePak's antioxidant and cardiovascular benefits are supported by two double-blind clinical studies. LifePak is intended for the general adult population and comes in two packets of four capsules each, to be taken with the morning and evening meals. All individual nutrient levels in LifePak are documented as safe, and clinical studies showed no adverse effects due to LifePak supplementation. Pregnant or lactating women, or individuals with known medical conditions, should consult a physician before using dietary supplements.

What Is LifePak®?

LifePak is a comprehensive dietary supplement, providing all essential vitamins and minerals, as well as antioxidant nutrients and phytonutrients, in optimum amounts to promote long-term health and general well-being.* LifePak is intended for healthy adults in general. Pharmanex also offers LifePak Women for premenopausal women, LifePak PreNatal for pregnant and lactating women, and LifePak Prime for men over age 40 and post-menopausal women. This publication covers regular LifePak.

Mechanism of Action

As a comprehensive nutritional multi-component product, LifePak has multiple mechanisms of action, which are described below whenever appropriate.

Scientific Studies

Clinical Studies

The ingredients of LifePak—vitamins, minerals, and phytonutrients—are supported by hundreds of well-designed clinical studies. Many of these studies are referenced in the Health Benefits section listed further on.

Unlike other multivitamin/mineral products, LifePak is also supported by two double-blind, placebo-controlled clinical studies, a 140-subject parallel design study, and a 46-subject crossover study. Both studies tested the antioxidant effects of LifePak in healthy non-smokers.

In the completely randomized crossover study,[1] a total of 50 healthy non-smokers were enrolled in the Evansville, Indiana area. The subjects did not take any antioxidant supplements or drugs other than the study products three months prior and during the study, and they consumed typical U.S. diets with less than five servings of fruits and vegetables per day. For six weeks, twenty-five subjects received LifePak, and 25 received a placebo. After a six-week washout period, the treatments were reversed, so that each subject served as his/her own control. Blood samples were taken at the start and end of each treatment period and analyzed for serum antioxidants and LDL oxidizability. Four subjects dropped out, three of them for reasons not related to the study, and one due to mild adverse reactions to the placebo treatment.

The results showed that LifePak significantly improved antioxidant status as evidenced by increased serum concentrations of ascorbic acid (from 68.1 ± 24.8 to 94.3 ± 26.4 µmol/L, $p \leq 0.001$; means ± SD, n=46); β-carotene (from 335 ± 197 to 716 ± 429 nmol/L, $p \leq 0.001$); α-carotene (from 77 ± 82 to 592 ± 364 nmol/L, $p \leq 0.001$); and vitamin E (a-tocopherol, from 20.0 ± 8.5 to 36.9 ± 13.0 µmol/L, $p \leq 0.001$), with no changes in placebo treatment.

Most important, LifePak significantly decreased LDL (low-density lipoprotein) oxidizability, as the lag time was prolonged (by 17%; $p \leq 0.001$), and oxidation rate was reduced ($p \leq 0.001$) without changes with placebo treatment. LDL oxidizability is believed to be an important factor in cardiovascular health, because oxidized LDL tend to adhere to the inner arterial wall more than non-oxidized LDL that are protected by antioxidants.[2]

This study concluded that LifePak significantly increased antioxidant status and decreased LDL oxidizability in healthy non-smokers consuming typical U.S. diets. Therefore, LifePak supplementation may have cardiovascular health benefits.* Results also confirmed the assumption that a complex antioxidant nutrient combination can be efficacious in the presence of a full spectrum of non-antioxidant nutrients in a nutritionally complete vitamin/mineral/phytonutrient supplement.

A second LifePak clinical study, the 150-subject parallel design study, was conducted in the Houston, Texas area, and confirmed the results obtained from the crossover study in essentially all measurements. Antioxidant status was significantly improved and LDL oxidizability was reduced, similar to the Evansville, Indiana study. Thus, the antioxidant and cardiovascular benefits of LifePak are supported by two independent, well-designed, double-blind clinical studies.

Health Benefits

General Well-Being

LifePak is formulated as a convenient dietary supplementation program addressing general health and well-being for a healthy lifestyle. As a result, LifePak supplementation offers many more health benefits than ordinary multivitamins, and all of these health benefits are important in maintaining good general well-being for life.* LifePak addresses the following important health issues: common nutrient deficiencies, anti-aging benefits, cardiovascular health, bone structure and function, insulin and blood glucose metabolism, immune function, and many others.* The following paragraphs review these health benefits.

Avoiding Common Nutrient Deficiencies

Large nutrition surveys show consistently that inadequate intakes of essential vitamins and minerals are common in the United States and other industrialized countries.[3–6] The Continuing Survey of Food Intakes by Individuals (CSFII) conducted by the U.S. Department of Agriculture (USDA) in 1994–96[3] showed that most people do not meet the Recommended Dietary Allowances (RDAs) for essential vitamins and minerals (see Figure 1). The most common nutrient deficiencies appear to be for the antioxidant vitamins A and E, vitamin B_6, the bone minerals calcium and magnesium, and the minerals iron—particularly for women— and zinc.[3] A large number of other studies document common nutrient deficiencies of vitamin D,[7] thiamin,[8–10] riboflavin,[11–14] vitamin B_6,[15, 16–22] folate,[23–25] vitamin B_{12},[15, 26–37] calcium,[5, 38] magnesium,[39–42] zinc,[3, 43–49] copper[50–56] and chromium.[55, 57–64]

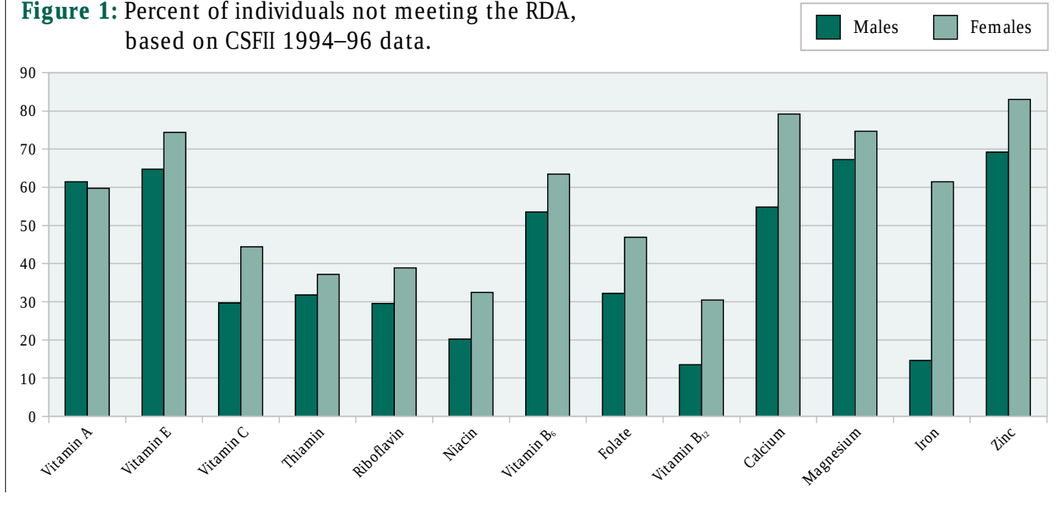
These common deficiencies in vitamin and mineral intakes can be attributed to the consumption of unbalanced diets that are low in fruits and vegetables[65, 66] and rich in energy-dense, nutrient-poor foods.[67] For example, an analysis by Block et al. of the National Health and Nutrition Examination Survey (NHANES II) data revealed that 41 percent of the population had no fruit on the survey day, only one fourth had a fruit or vegetable rich in vitamin A or in vitamin C, and only 10 percent consumed the recommended five servings of fruits and vegetables.[68]

Aside from eating more balanced diets rich in fruits and vegetables, LifePak supplementation ensures meeting the RDAs for all vitamins and minerals. The amounts of vitamins and minerals included in LifePak were chosen not only to prevent vitamin and mineral deficiencies, but also to correct any pre-existing deficiencies with regular use.*

Anti-Aging and Cell Protection Benefits

When discussing aging, it is important to separate age-associated diseases, e.g., heart disease, cancer, cataract, arthritis, Alzheimer's disease, etc., from the aging process itself, although the severity of age-associated diseases may be affected by the progression of the aging process. Aging itself is the result of normal developmental and metabolic processes involving the progressive loss of function that

Figure 1: Percent of individuals not meeting the RDA, based on CSFII 1994–96 data.



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eventually leads to the death of an organism.[69] LifePak is designed to address the symptoms of the normal aging process and provides protection to cellular and mitochondrial DNA, as well as to the lipids in cell membranes and the nervous system. The following paragraphs describe how special nutrients in LifePak contribute to these profound anti-aging benefits.

The most important factor in the aging process is maintaining the normal structure and function of the genetic code of every cell, stored in the cell's nucleus in the form of large nucleic acid molecules called DNA (deoxyribonucleic acid). DNA replicates and controls the inheritable characteristics of all organisms. Deficiencies of vitamin B_{12}, folic acid, vitamin B_6, niacin, vitamins C or E, iron, or zinc can damage DNA by causing single- and double-strand breaks, oxidative lesions, or both.[70, 71] As described in the section above, most of these nutrient deficiencies are very common in our population and are thought to be contributors to the aging process.[70] According to Professor Bruce Ames of the University of California at Berkeley, "common micronutrient deficiencies are likely to damage DNA by the same mechanism as radiation, and many chemicals appear to be orders of magnitude more important and should be compared for perspective. Remedying micronutrient deficiencies is likely to lead to a major improvement in health and an increase in longevity at low cost."[70, 72]

Folic acid and vitamin B_{12} are essential for normal DNA production and cell regeneration throughout the life cycle.[72, 72–78] Supplements of vitamin C can prevent DNA damage and promote DNA repair.[79–81] Similar effects have been demonstrated in human and laboratory studies for other antioxidant nutrients provided by LifePak, such as lycopene,[82–86] other carotenoids,[87–89] vitamin E,[81, 90–92] alpha-lipoic acid,[93] green tea catechins,[94–97] quercetin,[96, 98–100] and soy isoflavones.[100, 101]

Duthie et al. tested the effects of combined antioxidant supplementation for 20 weeks with vitamin C (100 mg/day), vitamin E (280 mg/day), and β-carotene (25 mg/day), and demonstrated a highly significant ($P < 0.002$) decrease in blood lymphocyte DNA damage in both smokers and nonsmokers.[102] Other similar studies did not find significant reductions in DNA damage;[103, 104] however, this dichotomy of results can be explained by shortcomings in analytical methods, the types of biomarkers chosen, and problems in study design. Moreover, there are indications that phytonutrients from fruits and vegetables are more effective in protecting DNA than the antioxidant vitamins[89, 103] and that antioxidant vitamins are more effective when combined with such phytonutrients,[104] as in LifePak.

Mitochondria—the cell's powerhouses—play a key role in cellular aging.[70, 71, 105, 106] Mitochondria are small structures inside cells that convert the energy from food nutrients into usable energy forms for cellular metabolism and functions (such as ATP). This mitochondrial energy conversion process—also known as respiration—requires plenty of oxygen and generates free radicals as unwanted byproducts. As a result, mitochondria, and especially the mitochondrial DNA (their genetic material), are major targets of free radical attack.[105–107] Unlike the cell's nuclear DNA, mitochondrial DNA defects due to free radical damage are not always completely repaired and accumulate more rapidly with advancing age.[105–107] Levels of oxidative damage to mitochondrial DNA are several times higher than those of DNA in the cell's nucleus.[105, 108] Experimental studies show that mitochondrial aging may be prevented or slowed down by improving antioxidant nutrient intake.[70, 105, 108]

Alpha-lipoic acid is an antioxidant nutrient and mitochondrial enzyme cofactor that received particular attention in recent anti-aging research. Unlike other dietary antioxidants, alpha-lipoic acid has the unique ability to neutralize many different types of free radicals and to provide broad-spectrum support to the body's antioxidant network.[109, 110] Alpha-lipoic acid also promotes the body's production or regeneration of the two major intrinsic antioxidants, L-glutathione[111–113] and coenzyme Q10.[109, 114] Because of its universal antioxidant properties and involvement in mitochondrial protection, alpha-lipoic acid appears to be the most useful antioxidant supplement in addressing the oxidative stress and damage associated with the aging process.[70, 93, 109, 111]

Another important factor in normal aging is the prevention of lipid peroxidation, especially in the cell membranes, the brain, and the vascular system. Vitamin E is perhaps the body's most important fat-soluble antioxidant nutrient protecting healthy cells from oxidative free radical damage.[115, 116] Vitamin E is an especially valuable antioxidant in the lipid-rich cell membranes, where it prevents oxidation of unsaturated fatty acids by trapping free radicals.[73, 117] This helps stabilize and protect cell membranes,[118] especially red blood cells and tissues sensitive to oxidation, such as the eyes[119] and the arteries.[120–123] Many studies show that vitamin E supplementation prevents lipid peroxidation of blood lipoproteins, such as the LDL and VLDL.[122–125]

Alpha-lipoic acid appears to be an excellent antioxidant nutrient to help protect the highly polyunsaturated lipids in brain and nervous system tissues, as this effect has been demonstrated by numerous clinical and laboratory studies.[126–132] The neuroprotective functions of alpha-lipoic acid have been ascribed to its unique ability to cross the blood-brain barrier.[132]

The body's proteins also become increasingly oxidized as we age.[133] This is especially noticeable in the lens of the eye, where oxidized lens proteins can lead to senile cataract development and vision impairment. A number of human studies have shown that long-term supplementation with vitamins C and E can help protect eye lens and other proteins in the body from free radical damage associated with the normal aging process.[134–138]

In summary, LifePak with its 30 mg alpha-lipoic acid, 500 mg vitamin C, 300 IU vitamin E, 600 mcg folic acid, 30 mcg vitamin B_{12}, 175 mg flavonoids, 15 mg mixed carotenoids, and all other important micronutrients is optimally formulated to provide comprehensive protection of cellular and mitochondrial DNA and the body's lipids and proteins, which are key determinants of the aging process.* As a result, long-term dietary supplementation with LifePak can be expected to provide significant anti-aging benefits.*

Cardiovascular Health

LifePak addresses many aspects of cardiovascular health. LifePak is formulated to provide the recommended amounts of the key cardiovascular nutrients, such as vitamin E, vitamin C, carotenoids, flavonoids, vitamin B_6, folate, vitamin B_{12}, magnesium, and calcium. The clinical effects of LifePak supplementation on LDL oxidation—a key factor for cardiovascular health—have been reviewed in the Scientific Studies section above.

Thousands of scientific studies document the beneficial effects of individual antioxidant nutrients on cardiovascular health,[139] and a number of studies indicated that combinations of antioxidant vitamins, carotenoids, and flavonoids are believed to be more effective than supplementation with any of these nutrients alone.[1, 140–142] LifePak is such a combination. The nutrients provided by LifePak have been shown to promote healthy vascular function and to support normal blood pressure, heart function, and microcirculation.* The following paragraphs show which nutrients in LifePak contribute to these cardiovascular benefits.

Vitamin E has been intensively studied, and most experts agree that daily dietary supplementation with 100 to 400 IU vitamin E has long-term cardiovascular benefits.[143–145] Chan provided an excellent review of the mechanisms by which vitamin E exerts its protective effects.[146] One such mechanism is improving the resistance of LDL against free-radical–induced oxidation.[2] Numerous clinical studies demonstrated that vitamin E inhibits LDL oxidation.[122, 147, 148] Likewise, the study by Smidt et al. showed that LifePak significantly decreased LDL oxidation, and this decrease was correlated to the response of vitamin E blood serum levels.[1] Vitamin E exerts its cardiovascular benefits also through other mechanisms, including the regulation of adhesion of blood platelets, monocytes, and T lymphocytes to the vascular endothelium, affecting endothelial fatty acid (eicosanoid) metabolism, smooth muscle cell proliferation, and platelet function.[146, 149] Recent clinical studies provided evidence that vitamin E supplements can help promote normal arterial wall function and thickness.[150–152]

LifePak provides vitamin E derived entirely from natural sources. The natural d-α-tocopheryl acetate and d-α-tocopherol used in LifePak are about twice as bioavailable as the synthetic dl-α-tocopherol used in other leading brand multivitamins.[153–156] In addition to d-α-tocopherol, LifePak also provides mixed natural tocopherols and tocotrienols. The level of 300 IU of vitamin E in LifePak is many times above the RDA (22 IU) or Daily Value (30 IU) and is supported by numerous human supplementation studies that show significant health benefits at daily vitamin E intakes between 100 and 400 IU.[139, 143–145, 157]

Vitamin C (ascorbic acid) is another antioxidant nutrient with cardiovascular benefits at above-RDA amounts.[158–160] This is supported by research that shows that vitamin C interacts and regenerates vitamin E in the body,[161, 162] and by clinical studies that demonstrate that vitamin C supplements can inhibit LDL oxidation,[125, 163] promote normal blood pressure,[164–168] blood lipids,[165, 169] coronary microcirculation,[170] and vascular endothelial function.[171–177] In addition, numerous epidemiological studies show strong associations between cardiovascular health and vitamin C intakes or blood serum levels.[160, 178, 179, 179, 180, 180–182]

Most human vitamin C supplementation studies used 100 to 1,000 mg per day, and pharmacokinetic studies by Levine et al. show that in healthy people blood serum concentrations plateau at dietary intakes above 200 mg per day.[183, 184] Based on these studies, LifePak provides 500 mg vitamin C in the form of calcium ascorbate, a well-tolerated, non-acidic form of vitamin C.

Carotenoids are a class of phytonutrients with many important nutritional and biochemical functions in mammals. Carotenoid intakes in the U.S. population are considered low, and reflect low fruit and vegetable

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consumption.[185] Epidemiological studies suggest that high carotenoid intakes from fruits and vegetables protect against cardiovascular disease.[186–188] However, the Physicians Health Study showed that 50 mg synthetic (all-trans) β-carotene taken every other day for 12 years produced no cardiovascular health benefits.[189] Current scientific evidence suggests that combinations of several carotenoids rather than mega-doses of synthetic β-carotene may exert the expected protective effects.[86, 186, 187, 190] Carotenoids other than β-carotene appear to have profound cardiovascular health benefits.[191, 192] Lycopene helps protect LDL from oxidation,[193, 194] and a-carotene[195, 196] and lutein[197, 198] may be protective as well.

LifePak provides a balanced carotenoid combination in amounts similar to those provided by diets high in fruits and vegetables: 6 mg β-carotene, 5 mg lycopene, 2 mg a-carotene, and 2 mg lutein.

Flavonoids form an important class of antioxidant phytonutrients with cardiovascular health benefits.[199] It is estimated that there are over 600 different flavonoids present in foods and beverages. Large epidemiological studies suggest that dietary flavonoid intake from fruits, vegetables, tea, grape juice, and red wine is positively associated with cardiovascular health.[200–205] Green tea catechins have been shown to decrease LDL oxidizability and total cholesterol.[206–210] Grape seed proanthocyanidins may support the resistance of LDL against oxidation.[211] Soy isoflavones may promote normal blood lipids, vascular function, and LDL resistance to oxidation.[212–219] Some research also supports that different flavonoids may have synergistic effects when combined.[220]

Estimates of average daily flavonoid consumption in industrialized nations vary from 20 to 100 mg per day.[221–223] LifePak provides an additional 175 mg of flavonoids from five standardized botanical extracts that all have been extensively researched: 90 mg green tea catechins, 25 mg quercetin, 25 mg citrus bioflavonoids (hesperidin, naringenin), 25 mg grape seed proanthocyanidins and polyphenols, and 10 mg soy isoflavones (genistein, diadzein).

The *B-vitamins*, B_6, B_{12}, and folic acid, are necessary to maintain normal, low blood levels of homocysteine. Homocysteine is an amino acid derived from methionine metabolism that can adversely affect lipid deposition and inflammation of the vascular wall.[224, 225] Many studies have established homocysteine as an independent risk factor for cardiovascular disease.[226–230] Current estimates are that about 10–15% of individuals are genetically predisposed to have high blood homocysteine.[231] Independently of its role in homocysteine metabolism, vitamin B_6 appears to have other benefits for cardiovascular health as well.[232]

Supplementation studies showed that primarily folic acid, but also vitamins B_6 and B_{12}, promote normal, low homocysteine levels.[233] Initially, pharmacological doses of folic acid, e.g., 1–5 mg/day, were used to lower homocysteine serum levels.[234] However, recent studies showed that as little as 200 µg/day folic acid is effective.[233, 235–237] LifePak provides 600 µg/day folic acid, 10 mg/day vitamin B_6 and 30 µg/day vitamin B_{12}; these levels are well within clinically effective doses to promote normal homocysteine levels.*

Magnesium deficiency is very common and characterized by cardiovascular symptoms.[73, 238] Magnesium influences many mechanical, electrical, and structural functions of cardiac and vascular cells, and small changes in blood or cellular magnesium levels may have significant effects on cardiac excitability and on vascular tone, contractility, and reactivity. This explains why magnesium is important in the physiological regulation of blood pressure.[239] A number of clinical studies support that supplemental magnesium can help promote normal blood pressure,[239–243] while some studies showed no effect.[244, 245] Magnesium may also be important in regulating thrombosis[246] and heart rhythm.[247, 248]

Calcium deficiency is a widespread problem with cardiovascular health implications. Adequate dietary calcium intake appears to be an important factor in promoting normal blood pressure,[249, 250] and this relationship has been sufficiently confirmed by clinical studies[251–253] and a recent meta-analysis of clinical calcium supplementation trials.[254]

The generous amounts of calcium (500 mg/day) and magnesium (250 mg/day) in LifePak ensure meeting the RDAs in conjunction with typical U.S. diets that are often low in these two minerals.[3, 38, 255]

Bone Nutrition

LifePak addresses bone health with a comprehensive array of bone nutrients, all present in nutritionally significant amounts: calcium, magnesium, vitamin D, vitamin K, boron, silicon, and soy isoflavones (phytoestrogens).

Undoubtedly, calcium has received the most attention as a bone nutrient.[256] Calcium is the major bone mineral and structural component in the form of calcium hydroxyapatite. Calcium supplementation can increase bone mineralization in children and young adults,[257–260] prevent bone loss in the elderly,[261, 262] and reduce the risk for osteoporosis.[260, 263–265] In fact, the FDA has approved the health claim for food and dietary supplements that adequate intakes of calcium, especially earlier in life, can slow the progression of osteoporosis later in life. Recently, the Food and Nutrition Board of the National Research Council announced new Adequate Intake (AI) values for calcium of 1,000 to 1,200 mg/day for adults.[266] Data from the USDA 1987–88 Nationwide Food Consumption Survey showed that mean per capita daily consumption of calcium for the total U.S. population was only 737 mg.[38] LifePak provides an additional 500 mg of calcium, which is the right supplemental amount to ensure that most individuals meet their dietary calcium requirements. Most other multivitamins supply considerably less calcium than LifePak.

As the second most abundant bone mineral, magnesium appears to be equally important for bone health as calcium,[267, 268] especially as marginal or inadequate magnesium intake is a significant concern in the U.S.[255] The 1996 USDA Continuing Survey of Food Intakes by Individuals (CSFII) showed that approximately three out of four adult women and two out of three adult men do not meet the RDA for magnesium.[3] Magnesium is involved in the regulation of calcium transport and metabolism,[269] and as such assumes a key role in bone formation.[267, 270] Magnesium deficiency has been shown to result in low bone mineral density.[267, 269, 271, 272] LifePak provides 250 mg of magnesium to ensure that the new RDAs of 320 mg/day for women and 420 mg/day for men[266] can be met easily.

The role of vitamin D in calcium and bone metabolism is well established.[273–275] There are a number of clinical trials documenting the benefits of supplemental vitamin D for maintaining normal bone health and calcium metabolism, especially in the elderly.[276–279] Although vitamin D is produced in the skin upon sunlight exposure, marginal vitamin D status is common especially in the elderly living in the northern latitudes of the United States and Canada.[274, 280–282] As a result, Holick recommended vitamin D supplementation from multivitamins in the amount of 400 IU daily.[282] LifePak provides 400 IU of vitamin D per day.

LifePak provides four other bone nutrients that are not typically found in other multivitamin/mineral supplements: vitamin K, boron, silicon, and soy isoflavones. Historically known for its role in blood coagulation, vitamin K is required for the formation of several calcium-binding proteins that are involved in bone formation, most notably osteocalcin.[283–288] It is now believed that adequate vitamin K nutrition is necessary to maintain bone health throughout life.[287, 288] Boron is thought to affect bone health by its involvement in steroid hormone metabolism.[271, 289] Among other factors, boron appears to be necessary for calcium and magnesium absorption, their adequate renal reabsorption, and their incorporation into the bone matrix.[73, 271, 289–300] Laboratory studies showed that silicon deprivation results in abnormal bone formation and skeletal malformations,[301–303] and reduces the incorporation of calcium and magnesium into bone.[304, 305] Silicon affects cartilage composition and cartilage calcification, the early steps in bone formation.[292, 301, 303] Experimental studies showed that silicon supplementation is able to promote bone formation as well as inhibit bone resorption.[306] The soy isoflavones genistein and daidzein support bone health by virtue of their roles as phytoestrogens.[307] Studies show that soy isoflavones appear to promote bone mineralization and may reduce bone resorption.[216, 308]

LifePak provides 40 µg vitamin K_1 (50% of RDI), 3 mg each of boron and silicon, and 10 mg of soy isoflavones, equivalent to approximately 10 grams of soy protein. Together with the significant amounts of calcium, magnesium and vitamin D, LifePak provides an exceptionally comprehensive approach in promoting healthy bone structure.*

Insulin and Blood Glucose Metabolism

LifePak provides nutritionally meaningful amounts of vitamins and minerals that promote normal glucose metabolism and insulin function already within the normal range.* Although LifePak is a dietary supplement and not designed to treat or prevent diseases, its high levels of antioxidant vitamins C and E, and the presence of significant amounts of alpha-lipoic acid, magnesium, zinc, and chromium, make LifePak an appropriate dietary supplement for people with insulin resistance, impaired fasting glucose, type 1 or type 2 diabetes mellitus, or metabolic syndrome X.*

Chromium is essential for normal insulin function.[73, 309–311] Clinical observations showed that the impaired glucose tolerance seen in patients receiving chromium deficient total parenteral nutrition could be reversed by supplemental chromium.[73, 312–315] It is now generally accepted that chromium acts as a cofactor for insulin.[73, 309, 310] The reported mechanism of action of chromium involves increased insulin binding, increased insulin receptor number, and increased insulin receptor sensitivity.[310] Chromium supplementation has been shown to promote healthy blood glucose metabolism without any documented side effects in a range of subjects, from people with mild glucose intolerance to overt type 2 diabetics.[310, 316] Many clinical studies show that

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chromium supplementation lowers blood insulin levels,[317] improves glucose tolerance,[317] and decreases hemoglobin glycosylation[317] in people with type 2 diabetes. It is believed that the positive effects of chromium supplementation are simply the results of correcting existing chromium deficiency, and do not involve pharmacological actions.[318, 319] Inadequate chromium nutrition appears to be widespread in the United States and other industrialized countries, and may affect as much as 90 percent of the U.S. population.[58] Most chromium supplementation studies in humans have used 200 µg of chromium daily,[309, 310] which is the same amount as provided by LifePak. The form of chromium in LifePak is a glycine-niacin-chelate (Albion Laboratories).

Zinc deficiency is also very common in people with diabetes[320–322] and is attributed largely to poor dietary intake and high urinary excretion.[323] Zinc may also promote normal insulin function by a more direct mechanism.[320, 324] Frequently, diabetic subjects are also at increased risk of magnesium deficiency,[325] which is due to low dietary intake and excessive urinary magnesium excretion.[326, 326–328] LifePak provides 15 mg zinc and 250 mg magnesium.

Antioxidant status is often low in patients with diabetes,[329, 330] and supplementation with antioxidant nutrients has resulted in significant nutritional benefits.[331] Such antioxidant nutrients do not treat or prevent diabetes, but address special nutritional requirements. For example, in many studies people with diabetes benefited from dietary supplementation with vitamin E, because it promoted normal platelet function,[332, 333] and provided antioxidant protection of the nervous system[334] and the body's proteins and hemoglobin.[332, 335–338] As a result, daily vitamin E supplementation has been recommended as part of a healthy diabetes diet.[331, 339] Diabetic subjects often have low serum vitamin C levels,[340–344] and vitamin C transport into the cell is impaired as well due to high sorbitol levels.[345] Sorbitol is a sugar-alcohol that accumulates inside the cells of diabetic people. Supplemental vitamin C is known to promote normal sorbitol metabolism[331, 346–349] and may also help maintain normal blood lipid levels[350] in diabetic subjects. LifePak provides clinically meaningful amounts of vitamin E (300 IU/day) and vitamin C (500 mg/day).

Alpha-lipoic acid supplementation of people with diabetes has been shown to significantly promote antioxidant protection and vitamin E status.[128, 351] Alpha-lipoic acid has the ability to cross the blood-brain barrier, so that it can exert its antioxidant benefits in the central and peripheral nervous system.[129, 132, 352] Numerous clinical studies document the ability of pharmacological doses of alpha-lipoic acid (600 mg/day) to promote normal peripheral nerve function in people with diabetes.[131, 353, 354] LifePak provides 30 mg alpha-lipoic acid, an amount considered appropriate for maintaining general antioxidant support in the nervous system (Lester Packer, Ph.D., personal communication).*

Immune Function

Since the immune system depends on adequate nutritional status of many vitamins and minerals, it is expected that LifePak effectively promotes healthy immune function in many ways.*

Deficiency of single nutrients results in altered immune responses, and this is observed even when the deficiency state is relatively mild. Vitamins A, C, E, and B_6, zinc, and selenium all have important influences on the immune system,[355, 356] and supplementation with these nutrients has been shown to improve immunity of populations at risk of deficiencies.[357, 358] The following paragraphs describe how each of these nutrients helps promote normal immune function.

Vitamin A is essential for maintaining a normal immune response.[73, 359] There appears to be a vicious cycle: during vitamin A deficiency, immune function is impaired[359] which puts the body at increased risk for infections.[360] Acute infections further deplete the body of vitamin A.[361] β-carotene may also promote normal immune function independently of its provitamin A functions.[362–365]

Numerous studies support that vitamin C supplementation can promote the normal immune response to occasional infections.[366–371] There is some evidence that during a cold infection vitamin C tissue requirements may be temporarily increased.[372]

Several clinical studies have confirmed the immune benefits of vitamin E in amounts of 100 to 400 IU per day.[366, 373, 374] Meydani et al. have conducted a study to determine whether long-term (235 days) supplementation with 60, 200, and 800 mg vitamin E enhances clinically relevant measures of cell-mediated immunity in 88 healthy elderly subjects.[375] Subjects consuming 200 mg/day of vitamin E had a 65 percent increase in delayed-type hypersensitivity skin response and a six-fold increase in antibody titer to a hepatitis B vaccine compared with placebo (17 percent and three-fold, respectively). The 200 mg/day group also had a significant increase in antibody titer to tetanus vaccine. Overall, results indicated that above-RDA vitamin E enhances clinically relevant indexes of T-cell–mediated function in healthy elderly persons.[375] LifePak provides 300 IU/day of natural d-α-tocopherol, equivalent to 201 mg.

Population studies showed that vitamin B_6 nutrition is associated with immune function.[376, 377] These findings were confirmed by human intervention studies which demonstrated that supplementation of elderly subjects with RDA-amounts of vitamin B_6 (2–3 mg/day) was able to restore normal immune function.[357, 378] Other studies showed similar immune benefits of vitamin B_6 at higher levels.[379, 380]

Zinc is known to play a central role in the immune system, and zinc-deficient people experience increased susceptibility to a variety of pathogens.[47, 381–388] Zinc also is important for normal wound healing.[389] Zinc affects multiple aspects of the immune system, from the barrier of the skin to gene regulation within lymphocytes. Zinc is crucial for normal development and function of cells mediating nonspecific immunity such as neutrophils and natural killer cells. The effects of zinc on these key immunologic functions is rooted in the myriad roles for zinc in basic cellular functions such as DNA replication, RNA transcription, cell division, and cell activation.[386]

Adequate selenium status appears to be necessary for normal immune function.[390–392] This may be due to selenium's functions as the cofactor for glutathione peroxidase,[390] or to more specific functions of selenium on cellular immunity.[392, 393] Good selenium nutrition also appears to be a requirement for normal anti-viral defense.[394–396]

Finally, there are studies that substantiate the clinical benefits of vitamin/mineral combinations on immune function. For example, Girodon et al. studied the effects of a combined supplement of 20 mg zinc, 100 mcg selenium, 120 mg vitamin C, 6 mg β-carotene, and 15 mg vitamin E in a study of 81 elderly people for two years, and found that the supplemented group had significantly fewer infections during the study.[397]

Other Health Benefits

Daily supplements of 400 µg folic acid have been widely recommended to women of childbearing age to prevent primary and secondary neural tube defects.[398–401] LifePak provides 600 µg folic acid per day.

LifePak is also an excellent supplement to help promote normal eye function, because it provides clinically meaningful amounts of nutrients that have been shown to protect ocular function as we age.* These nutrients include lutein,[134, 138, 402–409] vitamin C,[134, 138, 410, 411] and vitamin E.[136–138, 409, 410, 412–415]

With its 39 vitamins, minerals, and phytonutrients, LifePak has many more health benefits than the ones outlined here—too many to be discussed within the format of this monograph.

Side Effects

There are no known side effects of LifePak or any of its ingredients at the recommended usage levels. Likewise, a clinical study of LifePak in 46 healthy subjects conducted under FDA Good Clinical Practices guidelines revealed no adverse effects attributable to LifePak.[1] Similar observations were made in another, similar clinical study of LifePak in 140 healthy subjects (unpublished results).

Safety and Toxicology Data

Each ingredient in LifePak is present in amounts that are documented to be safe for long-term supplementation. The daily amounts of all vitamins and minerals are well below the No-Observed Adverse Effect Levels (NOAEL) established by the Council for Responsible Nutrition (CRN) in 1997[416] and the Upper Limits (UL) established by the Food and Nutrition Board of the National Research Council.[266, 417, 418] The other nutrients of LifePak, i.e., the phytonutrients, are added in amounts that can be obtained from diets high in fruits and vegetables (5–10 servings/day) or other commonly consumed foods and beverages. All of the phytonutrient extracts used in LifePak are documented to be safe and non-toxic. These extracts have been studied in humans at daily intakes similar or higher than those supplied by LifePak, and no significant side effects were reported.

Drug Interactions

Many drugs can alter the metabolism and bioavailablity of vitamins and minerals, and likewise—although much less frequently—some nutrients may also affect drug pharmacokinetics.[419, 420] For example, antituberculotic drugs such as INH and cycloserine interfere with vitamin B_6 metabolism and may also produce a secondary niacin deficiency. Oral contraceptives interfere with the metabolism of folic acid, ascorbic acid, and riboflavin. Anticonvulsants can act as folate antagonists and precipitate folic acid deficiency, and supplementation with folate has been recommended along with anticonvulsant therapy. Cholestyramine therapy has been associated with malabsorption of vitamins, such as vitamins K and D, and folic acid. Multivitamin supplementation has been recommended to avoid such adverse effects of drugs on nutrient metabolism. An excellent recent review of drug-nutrient interactions was prepared by Thomas.[419]

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One of the more frequent concerns among physicians is the potential interaction between vitamin K and anticoagulant drugs, such as warfarin and coumarin. However, significant reductions in efficacy of anticoagulant drugs require high-dose vitamin K supplementation of 250 µg per day or more.[421, 422] Anticoagulant therapy may also be affected by the daily variability in vitamin K intake from food rich in vitamin K, such as green leafy vegetables and broccoli which may contain up to 400 µg vitamin K per serving. As a result, diets with constant rather than low vitamin K content have been recommended for patients on anticoagulant therapy.[423, 424] LifePak provides 40 µg (50% RDI) daily of vitamin K, a level that has never been documented to interfere with anticoagulant therapy.

Proprietary Processing

The combination of quality ingredients, qualified manufacturers, certified independent laboratory verification, and a continuous drive to supply leading-edge products ensures our representatives and consumers the highest quality products available in the industry. LifePak is guaranteed to contain no added sugar, salt, wheat, dairy products, artificial preservatives, colors, or flavors.

The vitamins and minerals used in Pharmanex products meet the requirements and guidelines established by the United States Pharmacopoeia (USP) and/or Food Chemicals Codex (FCC) where applicable. Every batch of LifePak meets the USP XXIV requirements for capsule disintegration. All ingredients are tested for purity, and where applicable, ingredients are certified pure by microbial testing, such as tests for Salmonella, E. coli, other coliforms, Staphylococcus aureus, total plate counts, yeasts, molds, and pesticide residues. Our manufacturers go through a detailed selection and certification process to assure their compliance with Good Manufacturing Practice (GMP) standards set by the Food and Drug Administration (FDA).

Directions for Use

Take the contents of one LifePak packet with eight ounces of liquid with your morning and evening meals.

How Supplied

Each box provides 60 individual packets, or the equivalent of a one-month supply. Each packet contains one vitamin capsule, one phytonutrient capsule, and two mineral capsules.

Storage

Store in a cool, dry place, away from direct sunlight. Keep out of reach of children.

Shelf Life

LifePak is formulated to be stable at room temperature for at least two years from the date of manufacture.

Warnings

Keep this product out of reach of children. Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under six years of age. In case of accidental overdose, call a doctor or poison control center immediately.

Formula

The nutrient composition and ingredient sources of LifePak are listed below. LifePak is provided in two daily packets, each containing one vitamin capsule, one phytonutrient capsule, and two mineral capsules.

Eight capsules (= one daily supply in two packets) provide:	**Amount**	**%DV**[1]
Vitamin A (vitamin A palmitate)	5,000 IU	100
β-Carotene (from Palm fruit extract, *Blakeslea trispora*), 6 mg	10,000 IU	†
Vitamin C (calcium ascorbate)	500 mg	833
Vitamin D3 (cholecalciferol)	400 IU	100
Vitamin E (d-α-tocopheryl acetate, mixed tocopherols, and tocotrienols)	300 IU	1,000
Thiamin (mononitrate)	7.5 mg	500
Riboflavin	8.5 mg	500
Niacin (niacin, niacinamide)	40 mg	200
Vitamin B_6 (pyridoxine hydrochloride)	10 mg	500
Folate (folic acid)	600 µg	150
Vitamin B_{12} (cyanocobalamin)	30 µg	500
Biotin	300 µg	100
Pantothenic Acid (D-calcium pantothenate)	30 mg	300
Choline (choline bitartrate)	10 mg	†
Inositol	10 mg	†
Vitamin K_1 (phytonadione)	40 µg	50
Calcium (ascorbate, propionate, carbonate)	500 mg	50
Magnesium (magnesium chelate, oxide)	250 mg	62
Iron (iron chelate)	3 mg	16
Iodine (potassium iodide)	100 µg	66
Zinc (zinc chelate)	15 mg	100
Copper (copper chelate)	2 mg	100
Manganese (manganese chelate)	4 mg	200
Selenium (L-selenomethionine, sodium selenite)	140 µg	200
Chromium (chromium chelate)	200 µg	166
Molybdenum (molybdenum chelate)	75 µg	100
Vanadium (vanadyl sulfate)	20 µg	†
Silicon (sodium metasilicate)	3 mg	†
Boron (citrate)	3 mg	†
α-Lipoic Acid	30 mg	†
Carotenoid Blend (other than β-carotene):		
Lutein (from marigold flower extract)	2 mg	†
Lycopene	5 mg	†
α-Carotene (from palm fruit extract)	2 mg	†
Flavonoid Blend:		
Catechins (from *Camellia sinensis* leaf (20:1) extract)	90 mg	†
Grape Seed Extract (min. 95% polyphenols)	25 mg	†
Quercetin	25 mg	†
Citrus Bioflavonoids (from citrus fruits)	25 mg	†
Isoflavones (from soy extract)	10 mg	†

[1]U.S. Food and Drug Administration, Daily Values for nutrition labeling.
†Daily Values not established.

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*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

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